

July 24, 1973

MEMORANDUM FOR FILE

SUBJECT: Grant 734R2. (10937)
Carroll E. Cross, M.D.
"Effects of Tobacco Smoke on the Pulmonary Alveolar Macrophage -
Cytokinetic, Phagocytic Activities and Biochemistry."
Site Visit: July 9, 1973.

The co-investigators I saw were Elliot Goldstein, M.D., internist in charge of infectious diseases who trained at Channing, and was Huber's predecessor, and Mohammed G. Mustafa, Ph.D., trained in biochemistry. W. S. Tyler, formerly Professor of Anatomy in the veterinary school is now Director of the Primate Biology Laboratory and is also a collaborator indirectly. Mustafa and Cross have space there. Weekly seminars are held on pulmonary function problems for staff communication and for instruction of graduate and medical students taking research work. Actually one undergraduate premed was also working on monoamino oxidases in lysosomes. A general sense of collaboration was apparent. The medical departments were crowded in temporary laboratories. Construction of the basic medical sciences buildings will not begin until March of 1975. With 100 medical students per class the facilities will be crowded. Clinical facilities are now in Sacramento Hospital about 15 miles away. These facilities will be used until Medical Sciences II is constructed which will have 300-350 beds.

I first saw the Cross laboratories in the medical school and saw two students working there, one an undergraduate and the other, George York, a graduate. The latter was undertaking the experiment outlined for continuation.

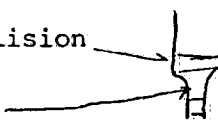
The Waltham was operating on 1 cigarette with 6 rats in holders that were much too large (guinea pig size for 35-45 gram rats, that were either with tails out of the groove and 2 were with noses in the tail groove. This was somewhat embarrassing. I don't think there is much of a constant dose here. The animal holders must be improved. The noses of the rats project too far into the chamber to permit the fan to work. Cross was anxious to have his men see a well-designed holder in function. He really needs holders of 2 sizes because of the ages at which he starts his animals. He does this because his other experiments on environmental health uses animals 1 week past weaning. Rats are pathogen-free at start.

Later I saw Ernie Bodai who was also smoking rats. He was using setup with Cambridge filters. Philip Morris cigarettes. Again I mentioned the reference cigarettes. Cross should be written about availability and costs of reference cigarettes. Bodai has his own filter -- a clever design of rapid propulsion and collision of particulates that seems to do a good job of particulate removal. It also traps H₂O and probably also H₂O-soluble gases.

1003539522

disc for acceleration and collision

filter to catch particulates



I repeated what Cross had been told that this was outside the area of cancer of the CTR. Bodai seemed an unusually bright and well-organized person.

Walter S. Tyler, Director, Davis Primate Center. He is a competent anatomist, em. and fem. person and has some excellent freeze etch specimens. His special area is studies on lung. He assumes that capillaries of bronchial arteries terminate in alveoli in some instances, differing from Liebow. The upper and lower lobes differ with more arterial perfusion of the upper lobes than the lower. Twelve years ago in Amer. J. Anat. he reported upper lobe vascularization with nicotine effects. He has now 2 freeze etch setups and 2 people to run them. He expends 40% of his time in laboratories.

Tyler is now working on Clara cells. They differ in different species. Rhesus monkey is much unlike man. The stub-tail monkey was most like man. Primate lab has 35 stub-tails on loan and is getting them back.

Dr. Neuratter, D.V.M., formerly at NIH is now at Davis as Associate Director and does all business administration.

Core facilities include virology, bacteriology, radiology, clinical chemistry, necropsy service, em. and sem. 80% of hard money goes to personnel.

Divisions:

Dr. Chapman, Behavioral studies.

Andy Hendricks, Paranatal biology.

Ernest Gardner, Congenital anomalies.

Dan Dunsworth, Pathology, including parasitology.

Oncology is being phased out. They have given their monkey lymphoma virus to other labs.

Nutrition nil now.

Genetics is interested in it from an animal breeding aspect. Blood group marker as a genetic starter.

Cross and Mustafa program. A student, Nancy Brunstater (?) developed ways of washing macrophages from mouse lungs and with marker chromosomes found that (1) bone marrow provides predecessors of lung macrophages, (2) that lung macrophages are viable for 3-4 weeks, and (3) that the lung macrophages may replenish themselves.

High O₂ consumption in lung macrophages, DPN dependent. Glucose depresses O₂ consumption. He reviewed the tobacco-water (saline) and the smoke in saline experiments. The latter were particularly toxic and decreased O₂, probably gas phase substances.

Similar O₂ depression is common to many toxic substances. Suggested that this might be a way to test for toxic cigarette exposure. (1) O₂, (2) O₃ & NO₂, (3) drugs - chemotherapeutic, (4) herbicides - paraquat, (5) cigarette smoke, and (6) circulating toxins.

Heinze body anemias, red cell effects of oxidants are also known. Modification of pentose shunt cause Heinze bodies.

1003539523

GSH - H₂O₂ → H₂O

GSH - GSSG - differs from cell.

The working hypothesis is that anti-oxidants might prevent non-specific damage of oxidants.

Tony DeLucca reviewed effects of GSH on O₃ exposure at toxic levels 2-4 ppm. Nothing protects against high doses. Small doses 0.8 ppm. increases SH in lung beginning at 2 days and persisting for 30 days.

Cross proposes to study enzymes in membraneous fraction and in cytosol to determine SH dependent protection. Mustafa stated that the cytochrome systems should be investigated.

Dr. Chow, Ph.D. Biochemist, is working on lipid metabolism particularly lipid proxides and peroxidases. A bioassay system has been developed.

Dr. Elliot Goldstein. His major interest is infectious diseases and he would include emphysema of some types here -- infectious complication of damaged lung tissue. He is working on macrophage effects on bacterial survival. Using staff he found normal macrophages inactivate bacteria quickly and stop division. Damaged macrophages do phagocytize but do not stop bacterial division. Clumps of bacteria occur in macrophages. He has an improved nebulizer -- over the Channing one -- a rather large apparatus. He has one graduate student working with him.

This is a multifaceted program with Carroll Cross as primary investigator. The people with him seem able and he is attracting some excellent students to work with him. He does need advice and direction on the use of the Waltham smoke exposure apparatus. I think it would be desirable to put on a demonstration for all investigators using them at the most recent possible date. Also animal holders should be designed for rats of different sizes. Even if the Waltham operates mechanically most effectively the animal holders will reduce effectiveness.

W.U.G.

WUG:ek

1003539524